

A case report of an unusual cause of mitral stenosis in a young woman

Ellie Senesael^{1*}, Danièle Plein², Mark La Meir³, and Steven Droogmans²

¹Department of Cardiology, University Hospital of Ghent, C. Heymanslaan 10, 9000 Ghent, Belgium; ²Department of Cardiology, Centre for Cardiovascular Diseases, University Hospital of Brussels, Laarbeeklaan 101, 1090 Jette, Belgium; and ³Cardiac Surgery, Centre for Cardiovascular Diseases, University Hospital of Brussels, Laarbeeklaan 101, 1090 Jette, Brussels, Belgium

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Background

Systemic lupus erythematosus (SLE) is an autoimmune disease, frequently associated with cardiovascular involvement. One of the most frequent complication is mitral valve regurgitation in more than one-third of the patients.

Case summary

A 30-year-old woman with arthralgia, butterfly rash, and Raynaud phenomenon presented with a systolic murmur and renal impairment. Based on the kidney biopsy the diagnosis of SLE was made. Echocardiography revealed the presence of pulmonary hypertension, restrictive mitral valve disease with nodular thickening of the anterior leaflet and moderate regurgitation, compatible with Libman Sacks (LS) endocarditis. Immunosuppressive therapy was started and the patient status improved with normalization of systolic pulmonary artery pressure. After 8 years without follow-up, she presented with fatigue and dyspnoea based on a severe mitral valve stenosis. Subsequently, she underwent a minimal invasive mitral valve replacement and the diagnosis of LS endocarditis could be confirmed upon histopathological examination.

Discussion

This case demonstrates that LS endocarditis can not only lead to mitral regurgitation but occasionally to mitral stenosis due to chronic inflammation with thickening and fusion of mitral valve leaflets. Hereby, comprehensive echocardiography, inclusive stress echocardiography, plays a critical role.

Keywords

Case report • Mitral stenosis • Systemic lupus erythematosus • Libman Sacks endocarditis • Stress echocardiography

Learning points

- Mitral stenosis in young patients is often due to rheumatic fever.
- Systemic lupus erythematosus (SLE) leads infrequently to mitral valve stenosis. A good clinical evaluation and echocardiography plays a critical role in the diagnosis and follow-up of mitral valve disease caused by SLE.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease, frequently associated with cardiovascular involvement, such as valvular abnormalities, pericarditis, endocarditis, myocarditis, coronary and pulmonary vessel disease.^{1–3} Mitral valve lesions occur in more than one-third of the patients, mostly leading to mitral regurgitation and rarely to mitral stenosis (MS).^{4–6} Here, we present a case of a 30-year-old woman with SLE symptoms and mitral regurgitation eventually leading to MS.

*Corresponding author. Tel: +32 476 32 59, Fax: +32 477 68 51, Email: esenesa@gmail.com. This case report was reviewed by Nisha Mistry, Monika Arzanauskaite, Christian Fielder Camm, and Peysh A. Patel.

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Timeline

Events	
December 2006	<p>Complaints of long lasting arthralgia, Raynaud phenomenon, and dyspnoea New York Heart Association (NYHA) Class II</p> <p><i>Physical examination:</i> cutaneous lesions, facial butterfly rash, and grade three systolic murmur</p> <p><i>Transthoracic echocardiography:</i> slight restrictive mitral valve motion with minimal thickening of the anterior mitral leaflet, moderate regurgitation and moderate systolic pulmonary hypertension (PHT) at rest; compatible with LS endocarditis</p> <p><i>Stress echocardiography:</i> no change in mitral regurgitation severity, forward gradient, or systolic PHT</p> <p><i>Immunosuppressive therapy:</i> cyclophosphamide and corticosteroids</p>
January 2007 to December 2014	Loss to follow-up
January 2015	<p>Complaints of fatigue and progressive exertional dyspnoea NYHA Class III</p> <p><i>Physical examination:</i> facial butterfly rash and grade five systolic murmur</p> <p><i>Transthoracic echocardiography:</i> more restrictive mitral valve motion, increased (nodular) thickening, reduced mitral valve opening (calculated mitral valve area of 1.0 cm²), stable moderate regurgitation, moderate systolic PHT at rest</p> <p><i>Bicycle echocardiography:</i> the severity of the mitral stenosis confirmed</p> <p><i>Immunosuppressive therapy:</i> high dose corticoids and cyclophosphamide were started in combination with hydroxychloroquine</p>
November 2015	<p>Mechanical mitral valve replacement was performed by minimally invasive port-access cardiac surgery</p> <p><i>Histopathology of the valve</i> confirms the diagnosis of LS endocarditis</p>
November 2016	Positive clinical evolution with a good exercise capacity and stable systemic lupus erythematosus under treatment with corticosteroids, mycophenolate and hydroxychloroquine

Case presentation

A 30-year-old woman presented with long lasting arthralgia, Raynaud phenomenon, and dyspnoea New York Heart Association (NYHA) Class II. Physical examination at the University Hospital of Brussels

revealed cutaneous lesions, a facial butterfly rash and a grade three systolic murmur. Laboratorial investigation revealed an elevated anti-nuclear antibody (ANA) (1:200, *normal range* $\leq 1:40$ is a negative test, $\geq 1:160$ is a positive test), in the absence of SLE-specific antibodies, reduction of complement factors C3 and C4 (48 mg/dL, *normal range* 93–177 mg/dL and 6 mg/dL, *normal range* 14–38 mg/dL, respectively) and severe renal dysfunction (CKD Stage 4, a creatinine of 2.4 mg/dL, *normal range* 0.4–1.2 mg/dL or an estimated glomerular filtration rate (eGFR) of 24 mL/min/1.73 m², *normal range* ≥ 60 mL/min/1.73 m²) with proteinuria. Subsequently, a renal biopsy was performed. A lupus nephritis Class II with mesangioproliferative glomerulonephritis was found. In addition, a skin biopsy confirmed cutaneous involvement.

Transthoracic echocardiography (TTE) demonstrated a slight restrictive mitral valve motion with minimal thickening of the anterior mitral leaflet-compatible with Libman Sacks (LS) endocarditis, moderate regurgitation (effective regurgitant orifice area 0.19 cm², regurgitant volume 39 mL), normal left atrial dimension (36 mm, 29.3 mL/m²), and moderate systolic pulmonary hypertension (PHT) of 45 mmHg at rest (*Figure 1A–C* and *Supplementary material online, Videos S1 and S2*).

Subsequent exercise echocardiography revealed an elevation in systolic pulmonary pressures from 39 to 53 mmHg without increased dyspnoea. Mitral valve (MV) gradients went from a peak and mean of 9/4 mmHg to peak and mean of 22/13 mmHg with a calculated mitral valve area (MVA) of 2.0 cm². Three-dimensional echocardiography confirmed the severity of the stenotic orifice with a MVA of 3.0 cm² (see *Supplementary material online, Video S1*).

Immunosuppressive therapy, with cyclophosphamide 500 mg intravenous every 2 weeks and methylprednisolone 64 mg daily for 1 week and afterwards a subsequent progressively decreasing dose, was started. Cyclophosphamide had to be interrupted after two cycles due to recurrent infections. Methylprednisolone 4 mg once a day (q.d.) was continued with clinical improvement (NYHA Class I) and normalization of systolic pulmonary pressure (24 mmHg) after 6 months. After 1 year azathioprine 100 mg q.d. was added to the treatment.

The patient was loss to follow-up during a period of 8 years until she presented with complaints of fatigue and progressive exertional dyspnoea NYHA Class III with a grade five systolic murmur and a facial butterfly rash upon clinical examination. Anti-nuclear antibody increased up to 1:1520 with anti-double stranded DNA (anti-dsDNA) 1:20 (*normal range* $\leq 1:10$ is a negative test). Furthermore, NT-pro-BNP was significantly elevated (10 066 ng/L, *normal range* 300–450 ng/L). Cardiac re-evaluation with TTE (*Figure 1D–F* and *Supplementary material online, Videos S3–S7*) demonstrated a more restrictive mitral valve motion with increased and nodular thickening of the anterior leaflet, reduced mitral valve opening with severe mitral valve stenosis (mean gradient of 6.1 mmHg and MVA 1.0 cm²) [0.7 cm² on three dimensional echo (see *Supplementary material online, Video S6*)], stable moderate mitral regurgitation, severe left atrial dilatation (48 mm, 59 mL/m²), a normal pericardium and moderate systolic PHT of 40 mmHg at rest. On apical four-chamber view (see *Supplementary material online, Video S4*) a ball-like density due to the nodular thickening of the anterior leaflet is appreciated.

A subsequent exercise echocardiography permitted us to confirm the severity of the disease since gradients are also flow dependent.

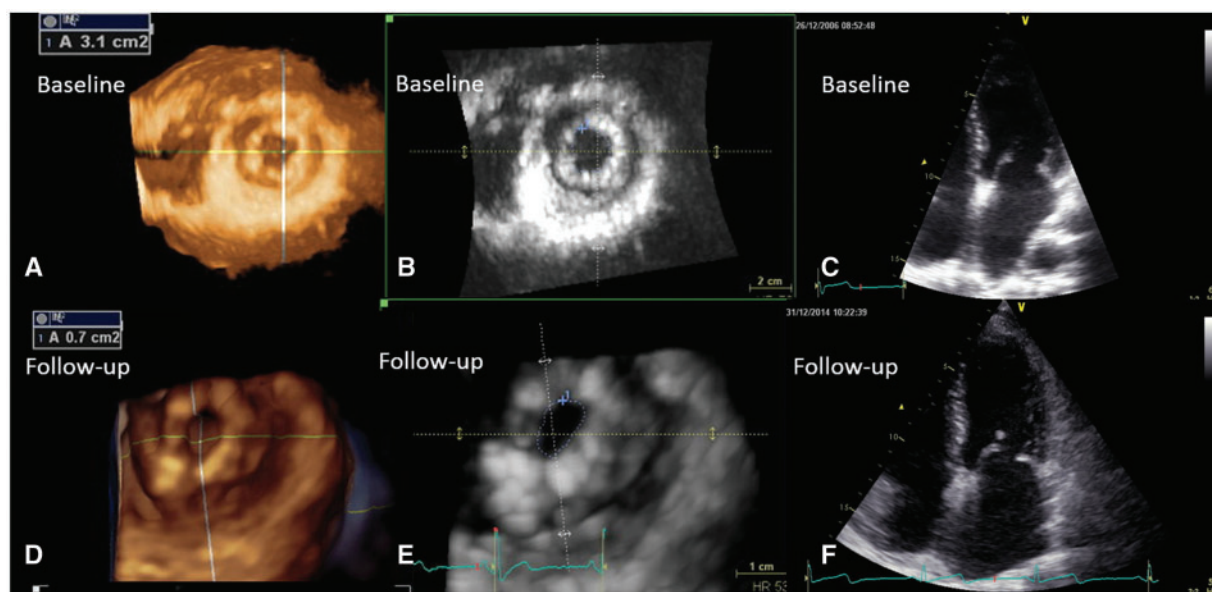


Figure 1 Two- and three-dimensional rest echocardiographical images from 2006 (baseline) to 2015 (follow-up) in a patient with systemic lupus erythematosus and progressive Libman Sacks endocarditis. (A, B, D, and E) Mitral valve area by planimetry of three- and two-dimensional planes in short axis are shown. (F) Reduced maximal diastolic opening (also see [Supplementary material online, Video S2](#)) with nodular thickening in 2015 compared with 2006 (C, see [Supplementary material online, Video S3](#)) on an apical four-chamber view is shown.

At 100 W a significant increase of mean MV gradients from 6.1 to 34 mmHg with an increase of systolic PHT from 40 to 67 mmHg and development of severe dyspnoea were appreciated ([Figure 2](#)).

A coronary angiogram with right heart catheterization showed normal coronary arteries and confirmed the moderate PHT of 40 mmHg.

Methylprednisolone 32 mg twice a day (b.i.d) and cyclophosphamide 500 mg intravenous, every 2 weeks for 3 months, were started in combination with hydroxychloroquine 200 mg b.i.d, bumetadine 2.5 mg q.d, and lisinopril 2.5 mg q.d.

Subsequently, a mitral valve replacement was performed by a minimally invasive port-access cardiac surgery (mechanical mitral valve St Jude Medical 31 mm). Histopathology of the valve showed fibrosis, neovascularization, inflammatory cell infiltration (plasma cells), and calcification, consistent with valvular involvement of SLE (LS endocarditis) ([Figure 3](#)).

Echocardiography after surgery showed a non-dilatated, normotrophic left ventricle with normal systolic function, mild left atrial dilatation (43 mL/m²), well-functioning mitral valve prosthesis (mean gradient 3.7 mmHg, MVA 1.4–1.5 cm²), and reduced right systolic PHT (23 mmHg).

One year later, the clinical condition of the patient was significantly improved with a good exercise capacity and stable SLE under methylprednisolone 4 mg q.d, mycophenolate 500 mg three times a day, and hydroxychloroquine 200 mg b.i.d.

Discussion

Systemic lupus erythematosus is more prevalent in women.¹ It is an autoimmune disease that can lead to multiorgan inflammatory damage through the formation and deposition of autoantibodies and immune complexes.^{1,2}

Cardiac involvement with pericardial and endocardial inflammation is frequently observed.³

In LS endocarditis, the mitral valve is most often affected, with mitral regurgitation occurring more frequently (25–28%) than MS (2.6–5.8%).^{4–9}

Mild inflammatory changes and fibrin-platelet thrombi adhered to the injured valve can lead to valve fibrosis, oedema, and diffuse thickening with valve degeneration as a consequence.⁷ Fibrin deposits, neovascularization, hyalinos, calcinosis, and a variable extent of inflammatory cell infiltration, especially mononuclear cells, can be found.⁷ These characteristics were also present in our case. These histological findings are however not specific as they are also seen in rheumatic heart disease.⁷ On the other hand, typical Aschoff bodies of rheumatic heart disease (due to rheumatic fever in the past) were not found.⁸

Mitral stenosis in young patients is predominantly caused by rheumatic fever in endemic regions.^{6,10} Differential diagnosis of MS in young patients in developed countries includes extensive congenital mitral annular calcification, systemic diseases (SLE,

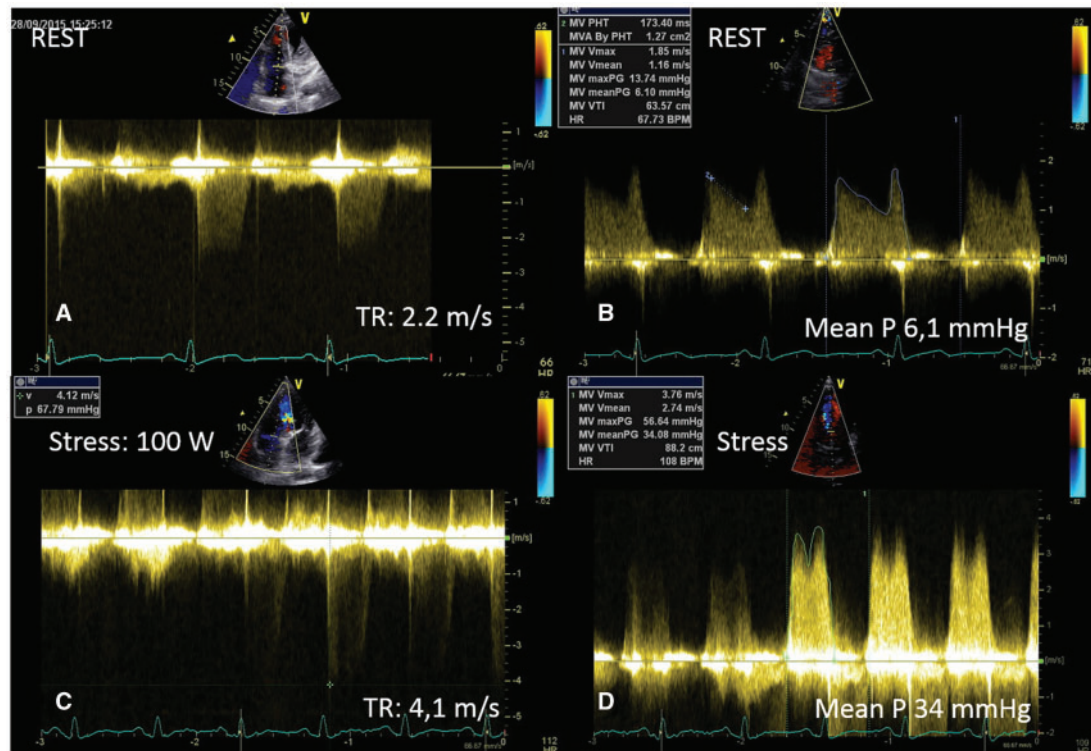


Figure 2 Bicycle echocardiography in 2015 at rest and during peak stress (100 W). Images show tricuspid regurgitant flow velocities (A and C) and continuous wave Doppler mitral velocities (B and D). Mean mitral valve gradient became much higher at peak stress (mean 34 vs. 6 mmHg) (D vs. B) with a significant increase in systolic pulmonary pressure (67 mmHg compared with 40 mmHg at rest) (C vs. A).

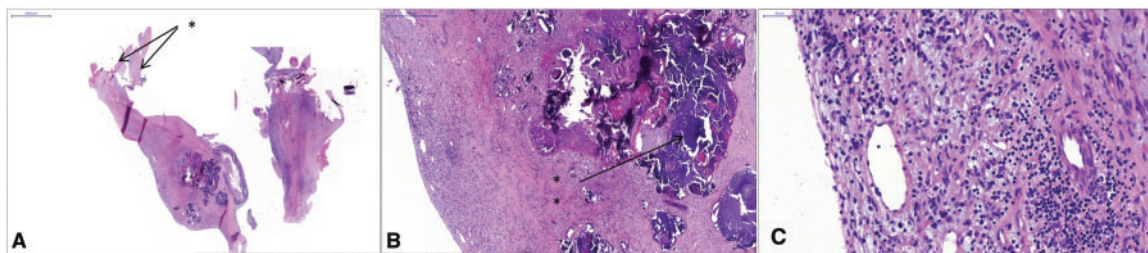


Figure 3 The excised mitral valve macroscopic view (A) shows the chordae tendineae (*) and mitral valve. Microscopic examination (B) shows the presence of distrophic calcifications (***) and strong widened collagen connective tissue and hyalinization. (C) neovascularization (typical for lupus) and chronic inflammation with plasma cells infiltration is shown. Haematoxylin and eosin stain, original magnification at $\times 10$ (A), $\times 50$ (B), and $\times 310$ (C).

Fabry disease, rheumatoid arthritis) and prior exposure to chest radiation.^{6,9}

The diagnosis of MS is based on echocardiography in which restrictive valvular motion is combined with reduced opening of the valve.¹⁰ Evaluation of MS is often difficult and several echocardiographic parameters need to be taken into account such as MVA planimetry, MVA continuity equation calculation (using transmitral diastolic pressure gradient and stroke volume), pulmonary pressures,

MVA, proximal isovelocity surface area method (PISA) for the resultant mitral regurgitation.¹¹ Three dimensional and biplane guided planimetry allow increased accuracy of the mitral valve area measurement.¹¹

In patients with systemic disease such as SLE, fatigue and dyspnoea are frequently present but a direct link to the severity of valvular heart disease is difficult to establish. In addition to a careful clinical evaluation (heart murmur, lung auscultation, jugular venous

distention, and the presence of oedema), NT-pro BNP, ANA, anti-dsDNA, complement C3 and C4, anti-Ro, anti-Sm and a comprehensive two- and three-dimensional echocardiography may be able to provide valuable additional information.^{2,6,12} Exercise echocardiography has the potential to evaluate the dynamic course of mitral regurgitation and stenosis and its effect on pulmonary pressures and symptoms.^{2,4} In our case, this was helpful in the decision leading to valve replacement.

According to recent ESC guidelines, cardiac MRI is of additional value, more specifically for quantification of valvular regurgitation. In addition, myocardial and pericardial catheterization might bring added value in systemic diseases. Also coronary computed tomography can exclude coronary artery disease in this patient population with intermediate cardiovascular risk whenever exercise test is inconclusive or not possible.⁶

One might speculate that the case we present would not have deteriorated towards severe MS as she had been more compliant to immune suppressive treatment. However, no studies showed clear relation between flares of SLE and the presence and severity of LS endocarditis. Moreover, even though corticoids reduce valvular inflammation and facilitate healing of valvular vegetations, they are known to also increase fibrosis and valvular deformation.¹³

The outcome seems good in most SLE patients who have undergone valvular surgery, but association of antiphospholipid antibody syndrome with SLE has negative impact on the outcome.^{14,15}

Conclusion

Severe MS is an infrequent complication of SLE (LS endocarditis). Comprehensive two- and three-dimensional echocardiography at rest and during stress are important for correct diagnosis and treatment of LS endocarditis.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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